Remarks/Arguments

Amendments to the Claims

Claim 13 is amended to define the length of the claimed oligonucleotide and to indicate that the claimed oligonucleotide specifically hybridizes to an allele at a selected polymorphic site or to a region of SEQ ID NO:1 that is one to several nucleotides adjacent to the polymorphic site. Support for this amendment is found in the specification at p. 12, lines 15-21, at p.14, lines 29-35, and p. 19, lines 2-7.

Claim 14 is amended to clarify that the claimed allele-specific oligonucleotide specifically hybridizes to an allele of the selected polymorphic site. Support for this amendment is found at p. 13, line 33 to p. 14, line 4.

Claim 15 is amended to clarify that the claimed oligonculeotide comprising a sequence selected from SEQ ID NOS:11-24 terminates at its 3' end with the selected sequence. Similarly, claim 17 is amended to indicate that the sequence of the oligonucleotide terminates at its 3' end with the selected sequence. These two amendments are supported in the specification at p. 13, line 37 to p. 14, line 3 and at p. 14, line 33 to p. 15, line 1, respectively.

Claim 20 is amended to clarify that the second nucleotide sequence is the complement of the first nucleotide sequence. Support for this amendment is found at p. 13, lines 7-9 and p. 27, lines 6-8.

Claim 24 is amended to clarify the structure of the claimed isogene fragment. Support for this amendment is found in the claim as originally filed and at p. 24, lines 20-22.

Claim 25 is amended to define the claimed polynucleotide as comprising a TNFRSF1A coding sequence or its complement; the coding sequence consists of SEQ ID NO:2 except for having an adenine at position 935 of SEQ ID NO:2. Support for this amendment is in the specification at p. 26, lines 17-24 and p. 27, lines 6-8.

Claim 28 is amended to clarify the structure of the claimed coding sequence fragment. Support for this amendment is found in the specification at p. 26, lines 26-27 and at p. 27, lines 6-8.

Claim 34 is amended to correct a lack of antecedent basis for "selected isogene"; support for this amendment is found in the claim as filed.

New claims 40-41 are presented. Claim 40 is directed to an isolated fragment which is the complement of the fragment of claim 24, while Claim 41 is directed to an isolated double-stranded fragment consisting of the isolated fragment of claim 24 and its complement. Support for claim 40 is found in the specification at p. 27, lines 6-8 and for claim 41 at p. 24, lines 12-14 and p. 27, lines 1-4.

New claim 42 is presented. Claim 42 is directed to an isolated double-stranded fragment consisting of a region of SEQ ID NO:2 including the novel allele at a position corresponding to nucleotide 935 and the complement of the region. Support for claim 42 is found in the specification at p.26, lines 26-27 and p. 27, lines 1-8.

New claim 42 is presented to define a kit in which the oligonucleotides have a minimum length. Support for this amendment is found in the specification at p. 12, lines 15-21.

New dependent claims 44 and 45 are presented, directed to the allowable subject matter identified in the Office Action. Support for these new claims is found in claims 20 and 34 as filed.

It is believed that no additional fees for claims are due, however if that is incorrect, Applicants hereby authorize you to debit deposit account 50-1293.

Claim Rejections

It is respectfully requested that the rejections to the claims be reconsidered and withdrawn in view of the remarks below.

Claim Rejections Under 35 U.S.C. §112, 1st paragraph

The Office Action rejects claims 24 and 28 under 35 U.S.C. §112, 1st paragraph for failing to comply with the written description requirement, noting that each of these claims encompasses additional variants that were not described in the specification as well as homologues and sequences from additional species.

Claim 24 is amended to clarify that the claimed isogene fragment is a fragment of one of the specific human TNFRSF1A isogene sequences discovered and described by Applicants, and which are recited in amended claim 20. Amended claim 24 also requires that the fragment include one of seven specific polymorphisms, which further defines the structure of the claimed fragment. Thus, as amended, claim 24 does not read on homologues or sequences from other species, and does not embrace variants of the isogene sequences of claim 20.

Similarly, claim 28 is amended to clarify that the claimed fragment is a fragment having at least 15 contiguous nucleotides of SEQ ID NO:2 that include position 935 of SEQ ID NO:2 with adenine substituted for guanine at position 935, or the complement of the fragment having at least 15 contiguous nucleotides of SEQ ID NO:2 that include position 935 of SEQ ID NO:2 with adenine substituted for guanine at position 935. Thus, as amended, claim 28 does not read on additional variants, mutations, homologues, or sequences from another species.

Since the Examiner's reasons for finding lack of written description are not applicable to claims 24 and 28 as amended, Applicants respectfully request reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §112.

Claim Rejections Under 35 U.S.C. §102

The Office Action has rejected claims 13-14, 16, 20 and 28 as being anticipated under 35 U.S.C. §102(a) by various oligonucleotides disclosed by Nandabalan et al. (WO 00/50436), noting that the

inventorship of WO 00/50436 and the instant application are different.

For a claim to be anticipated, a single publication must teach every limitation of the claim. (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379.)

The oligonucleotide of amended Claim 13 specifically hybridizes to (i) an allele of one of seven novel polymorphic sites in the TRNFRSF1A gene that were discovered by Applicants, (ii) the complement of the allele, or (iii) a region of SEQ ID NO:1 that is located one to several nucleotides downstream of one of these seven polymorphic sites. Dependent claims 14 and 16 further define the sequence of the claimed oligonucleotide. The Office Action states that the PCR primer of Nandabalan et al. denoted as SEQ ID NO:78 "is an isolated oligonucleotides that may be used to detect polymorphisms at PS4, PS12, PS14, PS15, PS17 and PS18." However this Nandabalan et al. PCR primer aligns with SEQ ID NO:1 of the instant application at nucleotide residues 3222-3249. The locations of the polymorphic sites recited in amended claim 13, PS1, PS4, PS12, PS14, PS15, PS17 and PS18, correspond to the following nucleotide positions in SEQ ID NO:1: 3102, 3603, 14824, 15089, 15093, 15932 and 16165. Residues 3222-3249 of SEQ ID NO:1 does not include any of the 7 polymorphic sites and it is located more than several nucleotides away from the 7 polymorphic sites. Therefore, it does not have a sequence that would specifically hybridize to the locations defined in amended claim 13. Consequently, Nandabalan et al. do not anticipate amended claims 13, 14 or 16.

Amended Claim 20 clarifies that the second nucleotide sequence is the complement of the first nucleotide sequence. The Office Action states that SEQ ID NO:79 of Nandabalan et al. "is complementary to position 3516-3536 of SEQ ID NO:2 of the instant application (limitations of Claim 20b)." Applicants presume that the reference to SEQ ID NO:2 rather than to SEQ ID NO:1 was a typographic error. SEQ ID NO:79 of Nandabalan et al. does not anticipate amended Claim 20 because it is an oligonucleotide that is only 28 nucleotides in length and complementary to only a small fraction of the first nucleotide sequence recited in Claim 20, which includes nucleotides 2920-4210, 11417-12926, and 14634-16768 of SEQ ID NO:1.

The Office Action states that Nandabalan et al. teaches ASO probes and primers for each of polymorphic sites PS2, PS3, PS5-PS11, PS13 and PS16. The Office Action points specifically to Nandabalan's SEQ ID NO:39 and Nandabalan's SEQ ID NO:15, each comprising 15 nucleotides comprising a T at position 224 of SEQ ID NO:2 (limitations of Claim 28), and states that Nandabalan teaches other 15-mers comprising an A at position 362 and a C at position 403 of SEQ ID NO:2. The isolated fragment of amended Claim 28 has a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO:2 that includes adenine at position 935. Adenine at position 935 in SEQ ID NO:2 was not disclosed in Nandabalan et al., therefore none of the ASO probes and primers of Nandabalan et al anticipate amended claim 28.

For the above reasons, Applicants therefore request reconsideration and withdrawal of the rejection of claims 13-14, 16, 20 and 28 as being anticipated under 35 U.S.C. §102(a) by Nandabalan et al.

The Office Action has rejected claims 13-17, and 20 as being anticipated under 35 U.S.C. §102(b) by one or more of Brennan (US 5,474,796), Hauptmann et al. (Genbank Accession A2908), Prashad et al. (WO 94/02500) and Brewer et al. (WO 97/31011).

As noted above, for a claim to be anticipated under 35 U.S.C. §102, a single reference must teach every element of the claim. (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379.).

The Office Action states that claims 13-14, 16 and 20 are anticipated by Brennan because Brennan teaches every possible 10-mer nucleic acid and an array of such 10-mers that would achieve the function of detecting a polymorphism. The oligonucleotide of amended Claim 13 is at least 15 nucleotides in length. Consequently, the 10-mers prophetically disclosed by Brennan do not anticipate claim 13, nor its dependent claims 14 and 16. As noted above, amended Claim 20 clarifies that the second nucleotide sequence is the complement of the first nucleotide sequence, which includes nucleotides 2920-4210, 11417-12926, and 14634-16768 of SEQ ID NO:1. However, no single 10-mer disclosed by Brennan is the complement of the first nucleotide sequence, and thus claim 20 is also not anticipated by Brennan. Applicants therefore request reconsideration and withdrawal of the §102(b) rejection of claims 13-14, 16 and 20 based on Brennan.

Claims 13-17 were rejected as being anticipated under 35 U.S.C. §102(b) by Hauptmann et al. (Genbank Accession A2908), who teach a 1368 residue coding sequence for TNFRSF1A. The oligonucleotide of amended Claim 13 has a maximum length of about 100 nucleotides. As the sequence disclosed by Hauptmann et al. is 1368 residues, Hauptmann et al. do not teach or disclose the oligonucleotide of Claim 13. Consequently, Applicants request that this rejection of Claims 13-17 be reconsidered and withdrawn.

Claims 13-14, 16-17 were rejected as being anticipated under 35 U.S.C. §102(b) by Prashad et al. (WO 94/02500), who teach a 25 residue oligonucleotide (Prashad et al.'s SEQ ID NO:47) comprising, as residues 3-12, the claimed SEQ ID NO:27. Claimed SEQ ID NO:27 is identical to residues 3593-3602 of SEQ ID NO:1, with its 3' terminus immediately adjacent to the nucleotide position in SEQ ID NO:1 corresponding to PS4. As noted, the oligonucleotide of amended Claim 13 specifically hybridizes to an allele of the selected polymorphic site, or its complement, or it specifically hybridizes to a region of SEQ ID NO:1, or its complement, located one to several nucleotides downstream of the selected polymorphic site. The 5'-3' alignment of Prashad et al.'s sequence with the genomic sequence of SEQ ID NO:1 in the region containing PS4 is shown below with PS4 bolded to demonstrate where Prashad's sequence is identical to SEQ ID NO:1 (underlines) and might possibly form Watson-Crick bonding with the complement of the genomic sequence, SEQ ID NO:1.

```
3581 to 3620 of SEQ ID NO:1  ttggtgtttg gttgggagtg gtaggattgg tgggttgggg
Prashad et al                             AGTGGGAGTG GTTACAAAAG CAGG
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As indicated by this alignment, only 14 nucleotides of the 25 mer disclosed by Prashad are identical

to a nucleotide in SEQ ID NO:1. In addition, the alleles observed at PS4 in SEQ ID NO:1 are S=G or C. However, residue 13 of Prashad et al's SEQ ID NO:47, corresponding to the position of PS4, is T. Thus, while the oligonucleotide of Prashad et al. might theoretically hybridize with the region of SEQ ID NO:1 containing PS4, it could not specifically hybridize to either allele of PS4, as required by the amended claims 13 and 14. Also, the Prashad oligonucleotide is identical to only 4 nucleotides of the 11 nucleotides located downstream of PS4 and thus would not specifically hybridize to this region or its complement, as required by the amended claims 13, 16 and 17. Consequently, Prashad et al. does not read on the claimed oligonucleotide of amended Claim 13-14, 16 and 17. Furthermore, the Prashad et al. oligonucleotides does not terminate in any one of SEQ ID NOS:25-38 as required by amended claim 17. For the above reasons, Applicants request reconsideration and withdrawal of the rejection of claims 13-14, 16-17 as being anticipated by Prashad et al.

Claims 13-14, 16-17 were rejected as being anticipated under 35 U.S.C. §102(b) by Brewer et al. (WO 97/31011), who teach an oligonucleotide comprising Applicants' SEQ ID NO:26. Brewer et al.'s oligonucleotide comprises a 21 residue oligo with the following sequence: CAGGTCCCCCTACACTAAGTG; Applicants' SEQ ID NO:26 is identical to residues 1-10 of the sequence of Brewer et al. Claimed SEQ ID NO:26 is the complement of residues 3103-3112 of SEQ ID NO:1, immediately adjacent to the nucleotide position in SEQ ID NO:1 corresponding to PS1. As noted above, the oligonucleotide of amended Claim 13 specifically hybridizes to an allele of the selected polymorphic site, or its complement, or it specifically hybridizes to a region of SEQ ID NO:1, or its complement, located one to several nucleotides adjacent to the selected polymorphic site. The region of SEQ ID NO:1 surrounding PS1 (bolded residue) is presented below in an anti-parallel alignment with the sequence of Brewer et al. with underlined nucleotides indicating which residues in the sequence of Brewer et al. are complementary to SEQ ID NO:1 and therefore capable of forming Watson-Crick base pairs with SEQ ID NO:1:.

```
3091-3120 of SEQ ID NO:1        5'tggggcaggg tkgggggacc tggccaggca 3'
Brewer et al.                    3'GTGAATCAC ATCCCCCTGG AC 5'
```

In SEQ ID NO:1, the observed alleles at PS1 were K=G or T. Note that within Brewer's sequence the position corresponding to PS1 has a T, and thus could not specifically hybridize to G or T at PS1 as required by the amended claims. Thus, while the oligonucleotide of Brewer et al. might theoretically hybridize with the region of SEQ ID NO:1 containing PS1, it could not specifically hybridize to either allele of PS1, as required by the amended claims 13 and 14. Also, the Brewer oligonucleotide is complementary to only 5 nucleotides of the 10 nucleotides located downstream of PS1 and thus would not specifically hybridize to this region or its complement, as required by the amended claims 13, 16 and 17. Furthermore, the Brewer et al. oligonucleotides does not terminate in any one of SEQ ID NOS:25-38 as required by

amended claim 17. Therefore Brewer et al do not read on amended Claims 13-14, 16 or 17 and Applicants request reconsideration and withdrawal of the rejection of claims 13-14, 16-17 as being anticipated by Brewer et al.

Claim Rejections Under 35 U.S.C. §103

Claims 18-19 are rejected under 35 U.S.C. §103 as being obvious over Brennan in view of Ahern (1995). Applicants thank the Examiner for promptly faxing a copy of Ahern to Applicants' Agent after it was noted to the Examiner that no copy of the reference was provided with the Office Action. It should be further noted that the reference is neither cited by Applicants on Information Disclosure Statement Form PTO/SB/08 filed November 16, 2001 nor by the Examiner on Form PTO-892 enclosed with the Office Action.

Claim 18 is drawn to a kit for haplotyping or genotyping the TNFRSF1A gene of an individual and comprises a set of oligonucleotides designed to haplotype or genotype each of the novel TNFRSF1A polymorphic sites disclosed in the application: PS1, PS4, PS12, PS14, PS15, PS17 and PS18. Claim 19 is a kit which additionally provides oligonucleotides to genotype additional TNFRSF1A polymorphic sites disclosed in the application: PS2, PS3, PS5-PS11, PS13 and PS16.

Brennan's patent provides a prophetic example teaching preparation of an array of all possible 10-mers, a total of 4^{10} (1,048,576) oligonucleotides. The Office Action states that Brennan therefore teaches every possible 10-mer oligonucleotide, including ones that could be included in the set of oligonucleotides in this kit for haplotyping or genotyping PS1, PS4, PS12, PS14, PS15, PS17 and PS18. The Office Action further states that while Brennan does not specifically teach packaging necessary reagents into a kit, Ahern teaches that kits save scientists time and money and therefore the ordinary artisan would have been motivated to have packaged the array of oligonucleotides of Brennan into a kit, as taught by Ahern, for the express purpose of saving time and money. Applicants assert that the Office Action fails to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991). Lastly, the prior art reference,or combination of references, must teach or suggest all the limitations of the claims. *In re Wilson* 424 F.2d 1382, 1385 (CCPA 1970). Further, the teachings or suggestions, as well as the expectation of success, must come from the prior art, not

applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

When applying §103, the "claimed invention must be considered as a whole" and "the references must be viewed without the benefit of hindsight vision afforded by the claimed invention". *Hodosh v. Block Drug Co., Inc.* 786 F.2d 1136, 1143, fn5; *MPEP* 2141.

Claim 18 is drawn to a kit. The claimed kit comprises a set of oligonucleotides to haplotype or genotype each of the novel TNFRSF1A polymorphic sites, PS1, PS4, PS12, PS14, PS15, PS17 and PS18, disclosed in the application. These recited polymorphic sites, which must be considered when considering the claimed kit as a whole, were not identified in the cited prior art as being sites where polymorphism existed. The cited prior art references of Brennan and Ahern, in the absence of Applicants' disclosure, do not provide motivation to select a set of oligonucleotides from the more than a million possible 10-mers disclosed by Brennan that are *designed* to haplotype or genotype the 7 specific polymorphic sites, where were unknown prior to Applicants disclosure, and to combine such selected oligonucleotides into the *claimed* kit.

Secondly, the cited prior art references, in the absence of Applicants' disclosure, do not provide any expectation of success in obtaining a kit to haplotype or genotype each of the novel TNFRSF1A polymorphic sites disclosed in the application. "[T]he references must be viewed without the benefit of hindsight vision afforded by the claimed invention". *Hodosh v. Block Drug Co., Inc.* 786 F.2d 1136, 1143, fn5; *MPEP* 2141. Since the polymorphic sites recited in claim 18 were not identified in the cited prior art as being sites at which polymorphism existed, there could have been no expectation that a packaged kit with Brennan's 10-mers would be successful as a kit to haplotype or genotype the novel TNFRSF1A polymorphic sites disclosed in the application in an individual.

Since, in the absence of the Applicant's disclosure of the polymorphism at TNFRSF1A polymorphic sites PS1, PS4, PS12, PS14, PS15, PS17, and PS18, there was no motivation to combine the cited references to obtain a kit of Brennan's 10-mers to haplotype or genotype these TNFRSF1A polymorphic sites and there could also be no expectation of successfully obtaining a kit to haplotype or genotype the TNFRSF1A polymorphic sites disclosed in the application by packaging the 10-mers of Brennan into a kit based on the teachings of Ahern, no *prima facie* case of obviousness has been established in the Office Action because at least two of the three requirements have not been met. Applicants respectfully request reconsideration and withdrawal of this rejection of claims 18-19.

Claim Objections

The Office Action objects to claims 21 and 35 as being dependent upon a rejected base claim. For the reasons discussed above, it is believed that amended claim 20 is patentable over the cited prior art. Applicants therefore request reconsideration of this objection.

The Office Action also objects to claims 21, 25, 34 and 35 as containing non-elected subject matter.

As claims 21 and 35 depend from claim 20, Applicants note that claim 20 must also contain non-elected subject matter, although this claim is not objected to in the Office Action. With respect to the objections to claims 21, 25, 34 and 35, Applicants note that the instant Office Action clarifies the restriction requirement mailed April 15, 2003, stating that claims 13-19, and 24 link inventions drawn to each of the isogenes, and that restriction between linked inventions is subject to nonallowance of the linking claims. The instant Office Action further states that upon allowance of the linking claim(s) the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or including all the limitations of allowable linking claim(s) will be entitled to examination in the instant application. It is believed, for the reasons discussed above, that claims 13-19 and 24 are now in condition for allowance. Applicants therefore respectfully request reconsideration of whether additional nonelected inventions linked by any of the allowable claims 13-19 and 24 are now entitled to examination, as well as reconsideration of the stated objection to claims 21, 25, 34 and 35.

Should any questions arise, or if Applicants or Applicants' Agent can facilitate examination of this application, it is respectfully requested that the undersigned Agent be contacted so that any remaining issues can be resolved.

Respectfully submitted,

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